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CASE REPORT

An Unusual Case of Concurrent Insulinoma and Nesidioblastosis

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ABSTRACT

Context Endogenous hyperinsulinaemic hypoglycaemia in adults is most commonly caused by an insulinoma. Adult nesidioblastosis is rarely reported. To the best of our knowledge the presence of both insulinoma and nesidioblastosis has not been reported before.

Case report We report a case of a 35-year-old female presenting with neuroglycaemic symptoms. A supervised 72-hour fast confirmed hypoglycaemia in the presence of hyperinsulinaemia. Thorough pre-operative biochemical and radiological investigations, including selective splenic, superior mesenteric and portal venous sampling inferred a tentative diagnosis of adult nesidioblastosis. However, a grossly elevated insulin level within the splenic vein on a second set of venous sampling produced a high index of suspicion for the presence of an insulinoma. At surgical exploration both an insulinoma and nesidioblastosis were identified and confirmed by histological examination.

Conclusion We report an even rarer entity of concurrent insulinoma and nesidioblastosis.

INTRODUCTION

Hyperinsulinaemic hypoglycaemia in adults is most commonly caused by an insulinoma. Laidlaw introduced the term nesidioblastosis nearly 70 years ago to describe diffuse proliferation of pancreatic islet cells budding from exocrine ducts [1]. Nesidioblastosis, whilst a well recognised disorder in infancy, is rare in adulthood and only a limited number of cases have been described [2]. We report an even rarer entity of adult-onset hyperinsulinaemic hypoglycaemia due to concurrent nesidioblastosis and insulinoma. To our knowledge, this is the first time that concomitant diagnosis has been recognised.

CASE REPORT

A 35-year-old female presented with a primary episode of acute psychosis during which her serum glucose level dropped to 0.7 mmol/L (reference range: 3.5-5.5 mmol/L). Following correction of hypoglycaemia her psychiatric symptoms resolved. During a supervised 72-hour fast she developed a hypoglycaemic episode with a serum glucose of 2.1 mmol/L, serum insulin of 52 pmol/L (reference value: greater than 36 pmol/L) and C-peptide of 340 pmol/L (reference value: greater than 200 pmol/L). Computed tomography, magnetic resonance imaging, an octreotide scan, endoscopic ultrasound and laparoscopic intra-operative ultrasound failed to identify an insulinoma. Initial selective venous sampling of the splenic, superior mesenteric and portal veins was inconclusive with only one slightly elevated insulin level of 679 pmol/L in the proximal portal vein (Figure 1). Repeat venous sampling six months later demonstrated one grossly

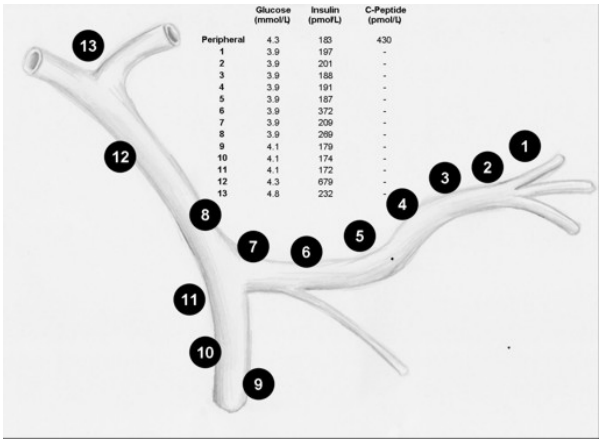

Figure 1. Initial selective portal venous sampling with measurement of glucose, insulin and baseline c-peptide. Proinsulins were not measured on this occasion.

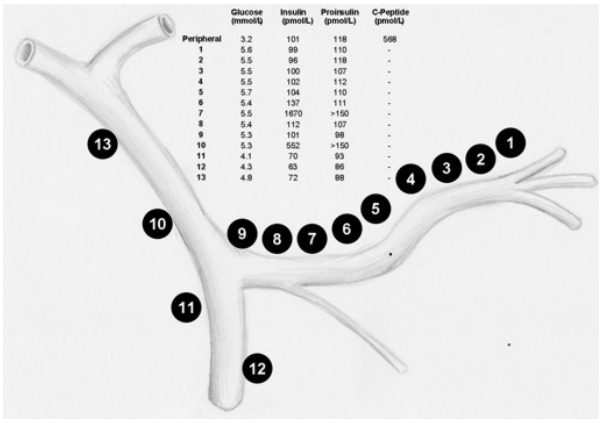

Figure 2. Repeat selective portal venous sampling with measurement of glucose, insulin, proinsulin and baseline c-peptide.

elevated insulin level of 1,670 pmol/L within the proximal splenic vein suggestive of insulinoma, but not conclusive (Figure 2). IGF-1 and IGF-2 levels were found to be within normal range.

An extended glucose tolerance test produced five readings below 3 mmol/L between 180-300 min, with a final reading of 2.1 mmol/L. Proinsulin levels were elevated at 133 pmol/L (reference range: 0-10 pmol/L) and a screen for sulphonylureas was negative. Insulin, pro-insulin and C-peptide were all measured using ELISA solid phase two-site enzyme immunoassay, (Merocdia AB, Uppsala, Sweden), with detection limits of 7.0 pmol/L, 0.5 pmol/L and 15 pmol/L, respectively. Having considered all the investigative findings, a tentative diagnosis of adult nesidioblastosis was made and the patient underwent an 85% distal pancreatectomy. However, because of the grossly elevated insulin level within the splenic vein (on the second set of venous sampling) a high index of suspicion for the presence of an insulinoma was maintained. A thorough macroscopic examination of the pancreas together with intra-operative ultrasound were therefore performed and an 8 mm lesion within the postero-inferior aspect of the pancreatic tail was identified. Intra-operative frozen section confirmed that this was an insulinoma (Figure 3). Further post-operative pathological analysis of the complete pancreatic resection specimen confirmed beta cell hyperplasia within enlarged pancreatic islets, containing pleomorphism and prominent nuclei consistent with nesidioblastosis and concurrent insulinoma of the pancreatic tail (Figures 4 and 5). Thirty months post-operatively the patient remains asymptomatic, with normal plasma glucose levels and has been discharged from follow-up. Insulin, pro-insulin and C-peptide levels were not measured post-operatively.

DISCUSSION

Insulinoma remains the most common cause of hyperinsulinaemic hypoglycaemia in

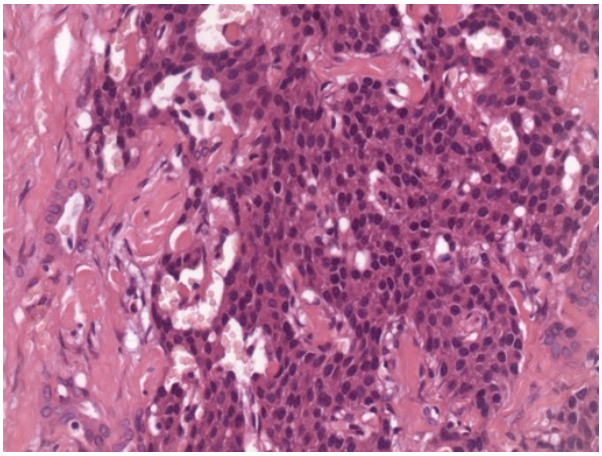

Figure 3. Histological specimen of insulinoma, (H&E staining, x200 magnification). A trabeculae of epitheloid cells and fibrous stroma, surrounding a central nuclei exhibiting pleomorphism. The cells stained positively for chromogranin, synaptophysin and insulin but negatively for somatostatin, glucagon and gastrin.

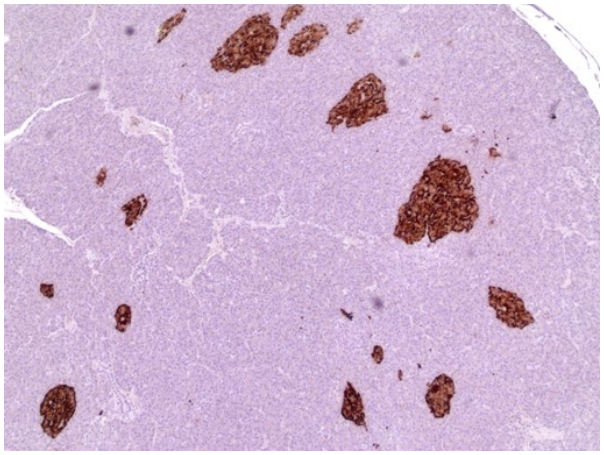

Figure 4. Histological specimen of pancreas (x200 magnification). Diffuse appearance of enlarged beta cells within the pancreatic islets, containing pleomorphism and prominent nuclei. Pancreatic islets stain positively for chromogranin.

adults. Nesidioblastosis is a well recognised cause of persistent hyperinsulinaemic hypoglycaemia in infancy but is rarely reported in adulthood. Recently, adult onset nesidioblastosis has become incorporated into the description of non-insulinoma pancreatogenous hypoglycaemic syndrome (NIPHS) [3] and there are 71 cases of adult nesidioblastosis in the literature with a reported prevalence between 0.5 and 5% [2].

The paucity of cases prevents the formulation of a definitive histopathological criteria for the disorder. Characteristically beta cell hypertrophy with enlarged and hyperchromatic nuclei in a lobulated islet cell arrangement are identified. Islet cells budding off exocrine ducts (ductuloinsular complexes) with neoformation of islets from ducts are also described [4]. As yet no single identifiable genetic defect has been detected [3, 5].

Clinical and biochemical differentiation between nesidioblastosis and insulinoma is problematic. Most patients have hypoglycaemic episodes occurring with fasting or exercise during which inappropriately high insulin and C peptide levels are recorded. The best diagnostic test for the detection of endogenous hyperinsulinaemia in adults is a supervised 72-hour fast. The test is positive if plasma glucose falls below 2.1 mmol/L, with concomitant serum insulin of greater than 36 pmol/L, C-peptide of greater than 200 pmol/L and proinsulin greater than 5 pmol/L [3]. The presence of post-prandial hypoglycaemic episodes has been suggested as diagnostic for nesidioblastosis [6].

Many insulinomas are small and hence are difficult to detect with conventional radiological pre-operative localisation studies such as CT, MRI, coeliac angiography and endoscopic ultrasound. Whilst there are reports of these investigative modalities being reliable [7], in this patient they were unhelpful since none of the pre-operative localisation studies identified the presence of an insulinoma, despite a positive 72-hour fast. When conventional radiological methods fail to confirm a diagnosis interventional approaches can be employed. Traditionally transhepatic venous sampling has been shown not only to confirm the presence of an insulinoma but is also able to locate tumours by demonstrating the elevation of insulin in samples obtained at specific sites along the portal, splenic and superior mesenteric veins. In one study of ten patients with insulinoma, Cho *et al*. [8] reported that tumours in the pancreatic head produced abnormal insulin elevation in venous samples obtained from the superior mesenteric and portal veins. Insulinomas in the pancreatic neck caused a

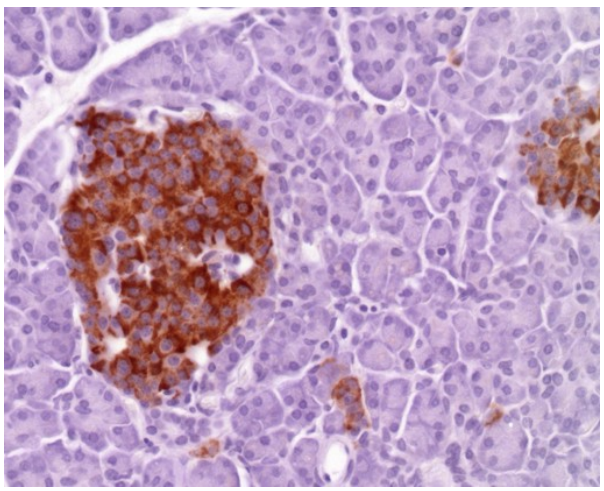

Figure 5. Histological specimen of pancreas (x400 magnification). Diffuse appearance of enlarged beta cells within the pancreatic islets, containing pleomorphism and prominent nuclei. Pancreatic islets stain positively for insulin.

step-up in the insulin concentration in the splenic vein near the confluence with the portal vein and superior mesenteric vein, whilst those occurring in the body and tail of the pancreas resulted in increased insulin levels within the splenic veins. The one patient with histologically proven nesidioblastosis showed abnormal insulin levels at several sites in the splenic, superior mesenteric and portal veins. In our patient selective venous insulin sampling detected neither increased insulin levels within the splenic vein suggestive of insulinoma within the pancreatic tail, or abnormal insulin levels at several sites throughout the portal, splenic or superior mesenteric veins suggestive of nesidioblastosis. Only one slightly elevated insulin of 679 pmol/L was detected within the proximal portal vein producing an inconclusive result. Although the repeat portal venous sampling produced a more pronounced elevation in insulin levels (1,670 pmol/L), this was an isolated reading rather than the typical step-wise progression of insulin concentration. More recently selective arterial calcium stimulation has been used for diagnosis of and pre-operative localisation of insulinoma in some centres. The sensitivity of this method has proved superior to that of selective venous sampling [9].

In most cases of endogenous hyper-insulinaemic hypoglycaemia, diagnosis and therefore treatment options depend on the combined results of clinical, radiological and intervention tests. A laparotomy is the usual end point of investigation at which a thorough macroscopic examination including bimanual palpation of the pancreas is performed. Unfortunately, when a discrete lesion cannot be identified, frozen section is rarely helpful in determining nesidioblastosis as the cause of the patient's hypoglycaemia. In this instance selective venous sampling or selective arterial calcium sampling can prove helpful in determining the extent of gradient guided surgical resection [6].

In our case the combined pre-operative tests suggested a diagnosis of nesidioblastosis and the decision had been made to proceed with an 85% distal pancreatectomy. The second portal venous sampling had alerted us the possibility of an insulinoma, which was confirmed at laparotomy. A review of the limited literature identified two previous cases of patients having diagnoses of both insulinoma and nesidioblastosis at separate intervals, but no cases of concurrent insulinoma and nesidioblastosis. One of the patients had histologically proven nesidioblastosis within the pancreatic body resected followed nine years later by enucleation of two insulinomas (5 and 15 mm) [10], whilst the second patient presented with recurrent symptoms of hyper-insulinaemic hypoglycaemia six years after enucleation for insulinoma, and subsequent distal pancreatectomy revealed nesidio-blastosis [11]. In our patient, if enucleation of the insulinoma alone had been performed, nesidioblastosis induced hyperinsulinaemic hypoglycaemia would have persisted post-operatively. Therefore, it is important to appreciate that concomitant nesidioblastosis and a functioning insulinoma may co-exist.

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Conflict of interest The authors have no potential conflicts of interest

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